MANNITOL THERAPY FOR ACUTE AND CHRONIC CIGUATERA FISH POISONING

DONNA G. BLYTHE, LORA E. FLEMING, D. RAM AYYAR, DON DE SYLVA, DANIEL BADEN AND KATHY SCHRANK

Blythe, D.G., Fleming, L.E., Ayyar, D.R., deSylva, D., Baden, D. & Schrank, K. 1994 08 01: Mannitol therapy for acute and chronic ciguatera fish poisoning. *Memoirs of the Queensland Museum* **34**(3): 465–470. Brisbane. ISSN 0079-8835.

An evaluation of Intravenous (IV) mannitol therapy for treatment of the marine toxin disease, Ciguatera Poisoning, in 107 persons from the South Florida/Caribbean area. 70 patients with ciguatera poisoning received IV mannitol treatment (1g/kg) within hours to 1000 days from exposure, and 37 patients with ciguatera poisoning received only supportive therapy, if any. The treated and non-treated groups were comparable, except for prolonged time until presentation of the untreated group. 29 out of 32 (91%) patients treated with mannitol within the first 48 hours from exposure had complete reversal of symptoms. Although not a formal randomized clinical trial, this case series does provide valuable information and support for the use of intravenous mannitol in the treatment of acute and chronic ciguatera poisoning.

Donna G. Blythe, University of Miami School of Medicine, Miami, Florida; Lora E. Fleming and D. Ram Ayyar, University of Miami School of Medicine, Miami, Florida; Don de Sylva and Daniel Baden, Rosenstiel School of Marine and Atmospheric Sciences, University of Miami, Miami, Florida; Kathy Schrank, University of Miami School of Medicine, Miami, Florida; *18 June 1994.*

Dinoflagellates in the marine genus *Gambierdiscus* elaborate a number of toxins which are bioconcentrated in the food chain through reef-feeding herbivores to larger predatory fish. When these larger species are eaten by humans, they lead to Ciguatera Poisoning. Ciguatoxin (CTX) is responsible for the majority of human illness associated with ciguatera poisoning (Carmichael et al.,1986; ILO,1984).

Ciguatoxin is a lipid soluble, heat stable and acid resistant neurotoxin (Carmichael et al.,1986, Sakamoto et al.,1987). It causes no adverse effects to the fish, and cannot be detected by differences in smell or taste, nor is it eliminated by cooking, freezing or other preparation procedures (Lewis,1986). The mechanism of action of ciguatoxin is as a sodium channel toxin (Lewis, 1986; Baden et al.,1990).

In the past, a variety of bioassays (including feeding and injections into cats, mongoose and mice) have been used to test for CTX in fish. Intraperitoneal injection in mice has been one of the most widely accepted bioassays, and more recently, rat brain synaptosome (Lange,1987; ILO,1984). In addition, to being impractical for routine use in the fish industry, there has been no test available for the evaluation of human ciguatera in clinical practice. Several new tests have been developed. One of these is a radioimmunoassay for ciguatoxin, a so-called 'stick test', which can be used to test for ciguatoxin in fish and has been widely used in Hawaii (Hokama, 1985). A highly sensitive ELISA test for assay in human biologic fluids is currently being trialled (Trainer & Baden,1990). Until these assays are established in human populations, diagnosis of ciguatera can only be arrived at clinically.

In the United States, nearly half of the reported foodborn disease outbreaks of chemical origin are due to marine toxins, with CTX causing at least one third of these outbreaks (Lange,1987). Ninety percent (90%) of the reported cases of ciguatera poisoning come from Florida and Hawaii (Lange,1987). In Miami, an average annual incidence of at least 5 cases/10,000 persons was estimated by reports to the Public Health Department and based on clinical diagnosis (Lawrence et al.,1980). In certain islands of the South Pacific up to 43% of the population has experienced at least one episode of Ciguatera (Rodgers & Muench,1986) and in Puerto Rico, up to 7% of the residents (Holt et al.,1984).

The human disease entity of 'Ciguatera Poisoning' is a direct result of the stimulation of adrenergic and cholinergic nervous system due to the opening of the sodium-dependent channels by ciguatoxin (ILO,1984; Lange,1987). It presents as an acute syndrome characterized by a variety of gastrointestinal, neurologic and cardiovascular symptoms within a few hours of contaminated fish ingestion. Most commonly, patients experience acute nausea, vomiting, diarrhea, gastrointestinal cramping, paresthesias, and bradycardia. Fatality, usually due to respiratory

TABLE 1. Subject characteristics in mannitol treatment study

Group	Number	Age (mean)	Sex (%Female)	Time Present	Sx	Fish
All	107	39y	48%	46d (0.3-1000)	12%GI 76% neuro	27%grouper 25%king
No Rx	37	41y	43%	111d (1-1000)	5%GI 92% neuro	40%king 27%grouper
Rx	70	39y	50%	11.5d (0.3-365)	16%GI 67% neuro	27%grouper 17%king
Rapid Rx	19	36y	56%	9d (0.4-70)	16%GI 42% neuro	63%grouper 11%barracuda
Slow Rx	51	38y	47%	12.5d (0.3-365)	16%GI 76% neuro	23%king 14%grouper

failure, cardiac arrhythmias and possibly cerebral edema, is reported to range from 0.1–12% of cases (Lange,1987; Morris et al.,1982; Bagnis et al., 1979). In addition to the acute illness, the chronic symptoms of ciguatera poisoning, especially the paresthesia, can persist in varying severity for months to years after the acute illness, with significant long term disability as a result. Chronic effects of ciguatera poisoning have been largely ignored in the literature, probably due to inaccurate diagnosis by inexperienced healthcare workers and lack of available human diagnostic testing (Lange,1987; Blythe & deSylva,1992).

A variety of treatment modalities have been tried for intervention in ciguatera poisoning. These include antihistamines, corticosteroids, calcium supplements, amitriptyline, fluoxetine, and lidocaine derivatives (Lange,1987; Berlin et al.,1992; Pearn et al.,1989; Gillespie et al.,1986). None of these therapies have withstood the test of time. 23 cases of clinically diagnosed acute ciguatera poisoning in the Marshal Islands were treated with an intravenous infusion of 20% mannitol (1g/kg at a rate of 500cc/hr) over 30 mins 'piggy backed' on an intravenous infusion at 30 cc/hr of either 5% dextrose in Ringer's or saline solution; there was complete resolution of symptoms within 48 hours in 17/23 patients (Palafox et al.1988). Pearn et al. (1989) published a case series of 12 patients treated with IV mannitol (0.5–1g/kg over 30mins); there were dramatic results in the 5 acutely ill patients. They postulated that mannitol might reduce axonal edema and/or act as a scavenger of hydroxyl radicals located on the ciguatoxin molecule.

We present a case series of 107 subjects with clinically diagnosed ciguatera poisoning from south Florida and the Caribbean collected since 1985. Seventy of these were treated with IV mannitol and 37 were not treated because they either presented prior to the Palafox publication, or mannitol was not offered or was declined.

METHODS

Patients of all ages and both sexes were diagnosed clinically with ciguatera poisoning if they gave a history of a) consuming reef fish from South Florida or the Caribbean and b) the onset of gastrointestinal symptoms within 6–24 hours of consumption and c) when relevant, subsequent onset of neurologic symptoms, usually after 24–48 hours from consumption. The gastrointestinal symptoms include nausea, vomiting, abdominal pain and cramps, and diarrhea; these gastrointestinal symptoms rarely last more than 48 hours from exposure with or without treatment. The neurologic symptoms reported include paresthesia (in the extremities and around the mouth) and weakness; these symptoms can persist upto 3 years in the case of one patient without treatment.

The patients were collected by two clinicians (DB, DRA) with known interest in ciguatera poisoning in the Miami (Florida) area from their clinical practice since 1985. A Ciguatera Network with referral telephone number had been set up by the authors to give advice and recommend treatment. Due to an ongoing research study, the following information was collected for each patient at presentation: age, sex, time from exposure until time of presentation, symptoms at presentation, and type of fish implicated.

Patients with clinical features consistent with either acute (ie. within 48 hours of exposure) or chronic ciguatera poisoning seen after the publication by Palafox et al. (1988) were offered mannitol treatment. Both clinicians gave mannitol in a dose of 1g/Kg; one clinician administered it over 3–4 hours (Slow) and the other over 30 minutes (Rapid).

Patients were asked to rate their response im-

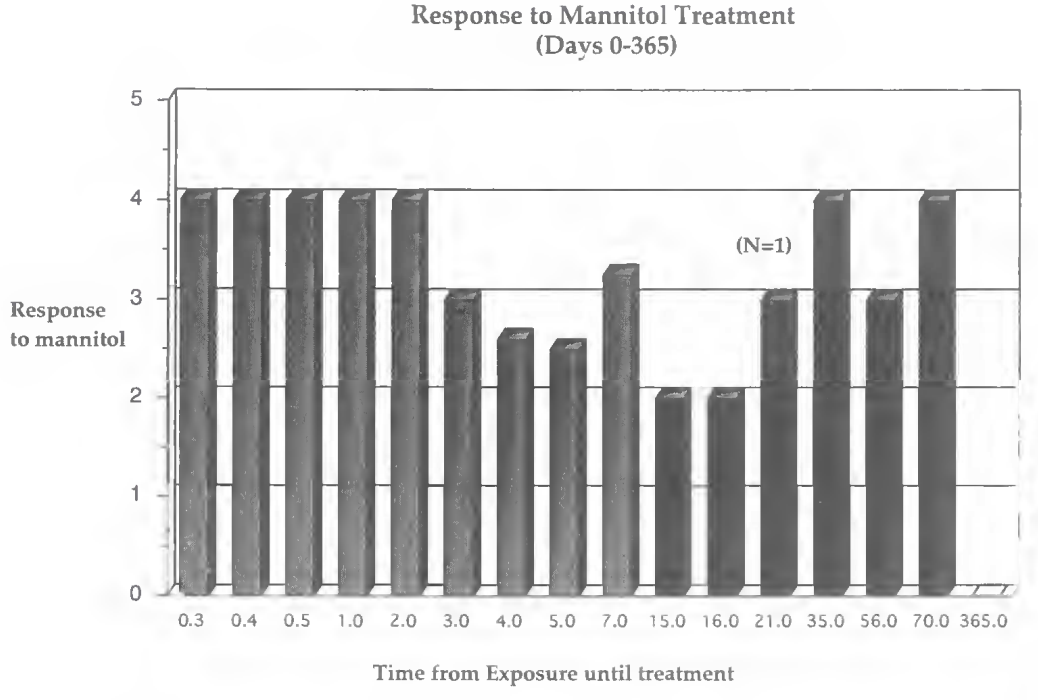

FIG.1. Response to Intravenous Mannitol Treatment (Days 0–356)

mediately after receiving the mannitol intravenous treatment (i.e. after 3–4 hours with the 'Slow' treatment and after 30 minutes with the 'Rapid' treatment). The responses were rated on a scale of 0 to 4+, in which 4+ meant recovery to normal without further treatment needed and 0 meant no change in their symptoms. In any case in which the reportedly positive effects of mannitol treatment did not last and neurologic symptoms returned, repeat treatments were offered under the same protocol until a 3+ to 4+ response was obtained and maintained.

Statistical analysis was performed on SE 30 MacIntosh using STATVIEW (Brainpower) statistical program.

RESULTS

Of 107 subjects, 70 (65%) were treated with mannitol (Table 1). 48% were women and 52% men with a mean age of 39 (± 15.9) and range of 1–79 years. The mean time from exposure to presentation was 46 days (± 149.5) with a range to 0.3–1000 days. Symptoms consisted of purely gastrointestinal in 12%, neurologic in 76% and combination of the two types in 12%. The pathognomonic symptom of cold to hot reversal was reported by the majority, but not all patients. The fish types reported were 27% grouper, 25% kingfish, 9% amberjack, 8% barracuda, 8% snapper, 8% other, and 15% unknown.

The symptoms at presentation had the following relationship to time from exposure: gastrointestinal symptoms alone were reported by those presenting within the first 24 hours, then both neurologic and gastrointestinal symptoms were reported by those presenting 24 hours from exposure until day 22, while neurologic symptoms alone were reported by those presenting after day 1 and up to day 1000 from initial exposure.

Of the 37 patients who did not receive any mannitol, there were 57% men and 43% women with a mean age of 41 (± 15.24), range 1–67 years. Their mean time to presentation from exposure was 111 days (± 235.3) with a range of 1–1000 days. The symptoms reported at the time of presentation were 5% gastrointestinal, 92% neurologic and 3% both; mannitol was not offered and no other intervention (ie. supportive) relieved these symptoms. Fish types identified

were 40% kingfish, 27% grouper, 11% snapper, 3% amberjack, 8% other, and 11% unknown.

70 patients were treated with IV mannitol. 50% were males and 50% females with a mean age of 39 years (±16.4), range 2–79 years. The mean time to presentation from exposure was 11.5 days (±44.5), range 3–365 days. The symptoms reported at the time of presentation were 16% gastrointestinal, 67% neurologic, and 17% both. Fish types reported were 27% grouper, 17% kingfish, 13% amberjack, 11% barracuda, 7% snapper, 10% other, and 14% unknown.

Of the 70 treated patients, 51 (73%) were treated with the 'slow' mannitol treatment and 19 (27%) by 'rapid' treatment. The mean overall response to mannitol treatment was a score of 3.3+ (±0.94) with a range of 0–4+. There were no adverse side effects reported to receiving mannitol treatment, either Rapid or Slow treatment.

32 (46%) of the 70 individuals treated within the first 2 days from exposure, 91% had +4 response, and 100% had 3+ or 4+ (Fig.1). There were 31 (44%) of the 70 individuals treated after day 2 through day from exposure; 23% had a 4+ response, 31% had a 3+ response and 35% had a 2+ response to mannitol treatment. Finally, 7 (10%) of the 70 treated individuals were 15 to 365 days from exposure; 33% had a 4+ response, 33% had a 3+ response and 33% had a 2+ response while the individual who was 1 year from exposure had no response to mannitol treatment.

As mentioned by Pearn et al. (1989), multiple treatments (mean 2 treatments, but up to 4 treatments) were required in five cases to maintain the initial positive response to treatment. All the multiple treatment persons presented within two days from exposure. There were no further reports of symptom recurrence or necessity for further medication from successfully treated patients after completing the mannitol treatments.

32 persons were treated within the first two days from exposure; 50% were male and 50% were female with a mean age of 31 years (range 2–60 years). Of these 32 persons, 28% reported purely gastrointestinal symptoms, 38% reported a mixture of gastrointestinal and neurologic symptoms, and 34% reported purely neurologic symptoms at the time of presentation. The majority (89%) of those persons reporting purely gastrointestinal symptoms at the time of presentation were 24 hours or less from exposure, while neurologic symptoms were reported after 24 hours from exposure.

Of the 51 patients treated by 'slow' mannitol treatment, there were 53% men and 47% women, with a mean age of 38 years (±17.7), range 2–79 years. The mean time to presentation (and treatment) was 12.46 days (±50.7), range 0.3–365 days. The presenting symptoms reported were 16% gastrointestinal, 76% neurologic and, 8% both. The fish types identified were 23% kingfish, 14% grouper, 14% amberjack, 12% barracuda, 10% other, and 19% unknown. The mean overall response to "slow" mannitol treatment was rated 3.1+ (±0.995), range 0–4+.

Of the 19 patients treated with 'rapid' mannitol treatment, 42% were men and 56% were women with a mean age of 36 years (±12.1), range 12–68 years. The mean time to presentation (and treatment) was 9.04 days (±19.3), range 0.4–70 days. The symptoms reported were 16% gastrointestinal, 42% neurologic, and 42% both. The fish types identified were 63% grouper, 11% snapper, 11% barracuda, 11% amberjack, and 5% other. The mean overall response to "rapid" mannitol treatment was rated +3.7 (0.56), range 2–4+.

By ANOVA analysis (Table 2), there were no differences between those with and without treatment with respect to sex (F=0.437, p=0.51), age (F=0.37, p=0.54), type of fish (F=1.67, p=0.19), and type of symptom (F=0.167, p=0.68). There was a statistically significant difference between those with (11.5 ±16.4 days) and without treatment (111 ±235.3 days) with regards to time to presentation from exposure (F=11.8, p=0.0008).

There was no difference by ANOVA analysis (Table 2) between the two treatment groups with respect to age (F=0.57, p=0.45), sex (F=0.638, p=0.43), type fish (F=1.37, p=0.246), time to presentation (F=0.081, and p=0.776). There was a statistically significant difference between Slow and Rapid treatment groups with regards to response to treatment (F=6.9, p=0.01) and type of symptoms at presentation (F=5.14, p=0.03), with Rapid treatment resulting in a better response.

By correlation analysis, positive response to mannitol treatment (ie. by the rating scale 0 to 4+) was correlated with the type of treatment (ie. Rapid vs Slow mannitol) (r=0.31) and time until presentation from exposure to contaminated fish (r=-0.442). By regression analysis in a model with the variables of type of treatment and time until treatment, both variables were statistically significant and predictive of successful response to treatment (F=12.6, p=.001).

DISCUSSION

Although not a random controlled clinical trial, treated and untreated patients with ciguatera

TABLE 2: Results of ANOVA Analyses of Treatment Group Outcomes

Group Treatment	Response	Age (mean)	Sex (%Female)	Time Present	Sx	Fish
Rx vs No Rx	N/A	F=0.37 p =0.54	F=0.44 p=0.51	F=11.8 p=0 .008*	F=0.17 p=0 .68	F=1.67 p=0 .19
Rapid Rx vs Slow Rx	F=6.9 p= .01*	F=0.57 p =0.45	F=0.64 p =0.43	F=0.08 p=0 .77	F=5.14 p=0 .03*	F=1.37 p=0 .25

poisoning from south Florida were identified which are comparable with respect to age, sex, type of symptoms, and type of fish consumed.

The only significant difference between the treated and untreated groups was that the treated group were more likely to present to the authors earlier in the course of their disease than untreated patients, even though the symptoms and disease entity were the same. We believe that the treated patients as a group presented earlier in the course of their illness due to new expectations for successful treatment and improved early diagnosis thanks to the community work in south Florida on ciguatera by these investigators. The majority of the persons in the untreated group had presented early in the course of their illness to other healthcare facilities and were treated unsuccessfully with a variety of treatments prior to being seen by the authors.

With regards to IV mannitol treatment, it appears to be effective in all ages and both sexes. There were no reported side effects to mannitol treatment. It is most effective if given within the first 48 hours from exposure. Mannitol treatment was moderately effective if given from 3–14 days from exposure (responses 2+ to 4+). In addition, based on data derived only from single individuals, moderate success was seen with treatment of individuals upto 70 days from exposure; the one individual treated 1 year from exposure had no response to mannitol treatment.

Multiple treatments (upto 4 additional treatments) were necessary in 5 individuals; there was complete resolution of symptoms with repeat treatments. The absence of interviewer blinding and of an objective measurement of response are weaknesses in this study. However, persons who reported a maintained successful response to mannitol treatment did not return for further treatment of any kind, while those who were not treated by mannitol continued to report symptoms even 3 years after exposure.

The prolonged symptoms with accompanying significantly increased time from exposure to presentation (mean 111 $\pm$235.3 days) among the untreated control group support the need to consider mannitol treatment for ciguatera poisoning, especially acutely. Although only a few individuals were treated after 14 days from exposure, in our experience it is worthwhile attempting mannitol treatment because it may relieve or even eliminate the debilitating neurologic symptoms of chronic ciguatera.

It appears that the more rapid administration (30 minutes) may be slightly more effective, although there were only 19 patients who received this treatment and as a group, they presented earlier in the course of the illness (9.04 vs 12.46 days) which correlates with a better response to treatment. However, the slow intravenous administration (over 3–4 hours) may be more appropriate with small children and others who cannot tolerate a heavy fluid load.

As opposed to the symptom course described in Pacific ciguatera poisoning (Bagnis et al., 1979), in our Atlantic experience the gastrointestinal symptoms universally preceded the neurologic symptoms. As such, it would be important to consider treatment with IV mannitol of any person presenting with the acute onset of gastrointestinal symptoms within 6–24 hours of consuming a large reef fish from a tropical area, even though the more classic neurologic symptoms have not yet presented.

Multiple fish types were reported in these ciguatera cases, although all were large reef fish species from tropical areas. Ciguatera poisoning has been associated with over 400 species worldwide. Also of interest to clinicians and epidemiologists, the ciguatera cases often presented in clusters due to sharing of fish among family and friends.

The social and economic impact of ciguatera poisoning, due both to the threat and the actual disease, is enormous. For example, in several highly endemic areas, local fish are avoided as a food source, as in south Florida where the sale of barracuda (a major source of ciguatera poisoning in the past) has been banned (Lawrence et al., 1980). Fear of ciguatera poisoning has lead to depression of local and exporting fishing industries and of tourism, and indirectly on human health due to avoidance of fresh fish consumption (despite its nutritional value) (Lewis,1986). The

impact of ciguatera and other marine toxins on the fishing industry is evidenced by the FDA Recommendations before Congress to require mandatory testing for marine toxins in all marine fish imported and sold in the United States.

Further work is needed on diagnosis, treatment and epidemiology of ciguatera poisoning. First, biomarkers in human fluids, as well as fish, are needed for the diagnosis and management of acute and chronic ciguatera poisoning. Animal studies of IV mannitol treatment are necessary to understand the mechanism of action. Random controlled double blind trials of IV mannitol in humans with biomarker-diagnosed ciguatera poisoning are needed. Biomarkers would be useful in determining the extent of acute and chronic ciguatera poisoning in humans worldwide. Finally, education of healthcare workers in endemic areas is crucial for the correct recognition and early intervention in ciguatera poisoning.

ACKNOWLEDGEMENTS

We acknowledge Ms. Susanne Cramer AB for her dedicated coordination of this project and Mr. Mauricio Ortiz MS for his statistical assistance. We would like to thank the patients who participated in this study.

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